Persistence With Growth Hormone Therapy in Pediatric Patients

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ABSTRACT

Objectives: Height outcomes were assessed in children with idiopathic growth hormone deficiency (IGHD) and multiple pituitary hormone deficiency (MPHD) who discontinued growth hormone (GH) therapy.

Study Design: Data were obtained from the American Norditropin Studies: Web-Enabled Research (ANSWER) Program/NovoNet for enrolled children who had discontinued therapy.

Methods: Treatment duration (months), height velocity, and corrected height standard deviation score (HSDS) at last clinic visit were evaluated; GH persistence rates were based on diagnosis (IGHD or MPHD) and discontinuation category.

Results: Patients who had achieved final height were on GH longer (46 ± 21 months, n = 288) than those who discontinued due to patient/caregiver decision (35 ± 15 months, n = 134), insurance issues (32 ± 21 months, n = 231), and other reasons (31 ± 18 months, n = 173). HSDS and corrected HSDS increased from baseline to year 3 across all categories (P <.0001). At year 3, patients in the final-height-achieved category had greater corrected HSDS (−0.3 ± 0.90, n = 179) than those who discontinued because of insurance issues (−0.6 ± 0.81, n = 63; P = .027) and other reasons (−1.0 ± 1.03, n = 55; P = .0006), and had the highest percentage of individuals reaching an HSDS of −2 or greater (96.4%, n = 190). Individuals in the final-height-achieved category were most persistent with GH therapy (P <.001).

Conclusions: Patients who discontinued GH due to final height achieved had the highest persistence. Consistent insurance standards for GH therapy could improve persistence.

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Recombinant human growth hormone (GH) is used to treat growth failure in children due to GH deficiency (GHD) caused by either idiopathic growth hormone deficiency (IGHD) or multiple pituitary hormone deficiency (MPHD).[1-3] Prepubertal status, height velocity (HV) at 4 months, and baseline body mass index standard deviation score (SDS) have been shown to be positively correlated with change in height SDS (HSDS) over the duration of GH treatment, whereas baseline age, baseline HSDS, and baseline insulin-like growth factor I SDS are negatively correlated with change in HSDS in response to GH.[4,5] Attainment of near-adult height or final height in GH-treated pediatric patients is associated with uninterrupted GH treatment regimens started at the earliest possible age to optimize long-term height outcomes.[6,7]

The International Society for Pharmacoeconomics and Outcomes Research has defined *medication persistence* as "the duration of time from initiation to discontinuation of therapy" and *medication compliance* (synonym: adherence) as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[8] Together, persistence and adherence ensure an optimal response to GH treatment.[9-12] Multiple previous studies of GH treatment have analyzed the role of adherence in the response to GH treatment.[9-13] However, only 1 study of GH treatment examined the effect of persistence on the response to GH treatment.[13] Nonpersistent patients were defined as those who were receiving GH at the beginning of the study but then took breaks from treatment, ranging from periods of less than 1 month to more than 1 year, or former patients who had completely discontinued therapy.[13] Nonpersistent patients were identified at all compliance levels, from highly compliant to noncompliant.[13] Overall, 22% of adolescents and 15% of children were nonpersistent.[13] A lack of GH persistence may be due to physician advice, GH cost, insurance coverage changes, painful injections, patient-parent perception that growth

PRACTICAL IMPLICATIONS

This analysis of the ANSWER Program registry—an observational, noninterventional study—provides reasons for lack of persistence with growth hormone (GH) therapy and the effect on outcome in pediatric patients with GH deficiency (GHD), including those with idiopathic GHD and multiple pituitary hormone deficiency.

- A change in insurance coverage was the second-most common reason for discontinuation of GH therapy.
- Patients who discontinued therapy because of insurance issues were least persistent with therapy.
- Pediatric patients discontinuing therapy for any reason other than achievement of final height had worse height outcomes, consistent with a shorter duration of treatment.

has finished, adverse reactions, lack of expected response, and treatment fatigue.[13]

The objective of this study was to analyze data from the American Norditropin Studies: Web-enabled Research (ANSWER) Program to determine persistence rates and height outcomes of children with IGHD and MPHD who discontinued GH treatment.[14] The ANSWER Program is a noninterventional observational study that collects long-term GH effectiveness and safety information from more than 13,000 patients treated at 175 clinical sites since 2002.

METHODS

Study Design and Analysis Population

Participating clinics obtained informed consent prior to entry of patient histories and physical examination data abstracted from their medical records into the study using an online data-reporting tool in NovoNet, a Web-based research platform. In order to be enrolled in the ANSWER Program, a child must be receiving GH therapy with Norditropin (somatropin injection). At sites participating in the registry, an attempt is made to enroll all individuals receiving somatropin injection. Subjects receiving somatropin injection had laboratory monitoring, clinical visits, and dose adjustment at intervals according to routine clinical practice. Data were collected from each clinic visit. Data for this study were entered into the database between the beginning of data collection (2002) and the date of data cut (2010). Patients with IGHD or MPHD were 18 years or younger, were previously untreated with GH, and had discontinued GH therapy and enrollment in the ANSWER Program. The patients' reasons for discontinuing GH were evaluated at their last clinic visit. The treating physician reports the reason for stopping therapy in free text form. The reasons for stopping GH therapy entered by physicians into the free text form were consolidated into 4 categories for analysis: final height achieved, insurance issues, patient/caregiver decision, and other reasons. Final height achieved was expected to represent individuals who had slowing of growth or closure of growth plates. Insurance issues were expected to represent individuals who discontinued somatropin injection because insurance coverage of GH therapy was denied, the cost of the medication exceeded the capability of the family to pay despite insurance coverage, or there was an insurance-mandated change in medication due to formulary specifications. The "patient and caregiver decision" category was expected to include individuals who reached a height in or near the adult normal range and who either chose to discontinue therapy or received a recommendation to discontinue therapy from their healthcare provider. It is possible that this category included individuals who were no longer compliant with therapy. HSDS and corrected HSDS (HSDS minus target HSDS) were evaluated at baseline, year 1, year 2, year 3, and the last visit.[4,5] Patients were excluded if their baseline age was younger than 1 year or older than 18 years, or if baseline values were missing, deemed inconsistent, or implausible (ie, baseline height <35 cm or >200 cm; baseline HSDS <−5 or > +2).[4,5]

Measures and Analyses

Baseline characteristics were obtained according to diagnosis as entered by the clinical site based on the clinical impression of the treating physician. No specific diagnostic criteria were imposed by the ANSWER Program. Variables included sex, age, bone age, HSDS, target HSDS, corrected HSDS, and peak stimulated serum GH (nanograms per milliliter). The HSDS was calculated using formulas from the Centers for Disease Control and Prevention.[15] Target height was calculated from mean parental height plus 6.5 cm for males or minus 6.5 cm for females. The HV (centimeters per year) was calculated at last visit by assessing the difference in height between the last visit and the previous visit (ie, at least 6 months prior to the last visit) divided by the number of days between visits and multiplied by 365.25. Corrected HSDS described HSDS relative to genetic height potential. The percentage of patients who reached HSDS >−2 was also determined over time. Analyses were performed to detect differences in persistence between the IGHD and MPHD groups and among the 4 discontinuation categories (ie,

Table 1. Baseline Characteristics by Diagnostic Category

Characteristic	IGHD		MPHD		Overall	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
No. (%)	876 (92.8)	–	68 (7.2)	–	944 (100)	–
Sex (male/female)	639/237	–	38/30	–	677/267	–
Age, y[a]	876	11.8 ± 3.27	68	9.9 ± 5.22	944	11.7 ± 3.48
Bone age, y[b]	715	10.2 ± 3.09	38	9.7 ± 4.23	753	10.2 ± 3.16
HSDS[c]	876	−2.1 ± 0.85	68	−1.8 ± 1.19	944	−2.1 ± 0.89
Target HSDS[d]	749	−0.4 ± 0.83	47	0.1 ± 0.75	796	−0.3 ± 0.83
Peak GH, ng/mL[e]	628	6.0 ± 2.59	47	4.4 ± 3.99	675	5.8 ± 2.74

GH, growth hormone; HSDS, height standard deviation score; IGHD, idiopathic growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SD, standard deviation.
[a]Patients with IGHD were, on average, 2 years older than those with MPHD (P = .0038).
[b]Patients with IGHD had an average delayed bone age versus chronologic age of 1.6 years compared with 0.2 years in patients with MPHD.
[c]HSDS at baseline differed significantly between the IGHD and MPHD patient groups (P = .0213).
[d]Target HSDS at baseline differed significantly between the IGHD and MPHD patient groups (P = .0005).
[e]Maximal (peak) stimulated GH levels (nanograms per milliliter) were significantly higher in patients with IGHD than MPHD (P = .0125).

final height achieved, insurance issues, patient and caregiver decision, and other).

Statistical Analysis

Demographics and baseline characteristics of patients with IGHD and MPHD, and of patients in each discontinuation category, were summarized using descriptive statistics. Significant differences between patient group baseline characteristics were determined using independent sample t tests. A χ^2 test evaluated differences in sex proportions among categories. The percentage of patients remaining on therapy over time in each category was determined from Kaplan-Meier survival curves. Adjusted for baseline age and sex, persistence was estimated with a computerized statistical model for survival data using proportional hazards without censoring and the Kolmogorov-Smirnov test for comparisons among categories. The same model was applied to analyze persistence in patients with IGHD or MPHD. The HSDS and corrected HSDS were determined using a last-observation-carried-forward approach and tested for differences between each category using independent sample t tests. All reported values are mean and standard deviation (SD). Differences between means were considered significant at P <.05.

RESULTS

Patient Demographics and Baseline Characteristics by Diagnosis

An initial total of 944 patients with GHD (IGHD, n = 876; MPHD, n = 68) met the inclusion criteria (Table 1). The mean age at baseline was 11.7 ± 3.48 years and 71.7% of the patients were male (IGHD: 72.9% male; MPHD: 55.9% male). Patients with IGHD were, on average, 2 years older (11.8 ± 3.27 years) than patients with MPHD (9.9 ± 5.22 years; P = .0038), and had a greater average delayed bone age versus chronologic age (IGHD, 1.6 years; MPHD: 0.2 years). The HSDS and target HSDS at baseline differed between patients with IGHD and MPHD (HSDS: −2.1 ± 0.85 and −1.8 ± 1.19, respectively, P = .0213; target HSDS: −0.4 ± 0.83 and 0.1 ± 0.75, respectively, P = .0005). Maximal stimulated serum GH levels (nanograms per milliliter) were significantly higher in patients with IGHD than MPHD (6.0 ± 2.59 and 4.4 ± 3.99, respectively, P = .0125).

Baseline Characteristics by Discontinuation Category: Combined IGHD and MPHD

Baseline characteristics were analyzed in a reduced subset of 826 patients for whom reason for discontinuation of GH treatment was available. Individuals with IGHD (n = 778) or MPHD (n = 48) were combined and categorized based on reason for discontinuation of GH treatment (Table 2). Baseline characteristics were similar among all discontinuation categories except for chronologic age and bone age. The mean baseline chronologic age (9.9 ± 3.8 years; P <.0001) and the mean baseline bone age (8.8 ± 3.3 years; P <.0001) were lowest in the insurance-issues patient category. No statistically significant differences (P = .4563) occurred in sex distributions among categories (ie, final height achieved, 70.8% male; insurance issues, 75.8% male; patient and caregiver decision, 70.1% male; and other, 69.4% male). The most common reason for discontinuation was final height achieved (34.9%), followed in order by insurance issues (28.0%), other (20.9%), and patient and caregiver decision (16.2%). Nonadherence (3.6%), healthcare provider recommendation (3.3%), adverse events (2.5%), change of physician or patient moved (1.5%), or lack of response

Table 2. Baseline Characteristics by Reason for Discontinuation of GH Therapy: Combined IGHD and MPHD Groups

	Final Height Achieved		Insurance Reasons		Patient/Caregiver Decision		All Other Reasons	
Characteristic	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
No. (%)	288 (34.97)	–	231 (27.97)	–	134 (16.22)	–	173 (20.94)	–
Sex, n (male/female)	204/84	–	175/56	–	94/40	–	120/53	–
Age,[a] y	288	12.9 ± 2.25	231	9.9 ± 3.83	134	12.8 ± 2.86	173	11.7 ± 3.57
Bone age,[b] y	259	11.1 ± 2.34	192	8.8 ± 3.33	123	11.1 ± 2.73	148	10.2 ± 3.42
HSDS[c]	288	–2.1 ± 0.83	231	–2.2 ± 0.80	134	–2.1 ± 0.95	173	–2.2 ± 0.89
Target HSDS	258	–0.4 ± 0.85	191	–0.2 ± 3.14	110	–0.3 ± 0.79	140	–0.0 ± 3.46
Corrected HSDS	258	−1.8 ± 1.00	190	−1.8 ± 1.00	110	−1.8 ± 1.05	139	−1.9 ± 1.07
Peak GH,[d] ng/mL	240	5.5 ± 2.79	205	5.6 ± 2.80	116	5.0 ± 2.93	137	5.4 ± 2.88

Corrected HSDS indicates HSDS minus target HSDS; GH, growth hormone; HSDS, height standard deviation score; IGHD, idiopathic growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SD, standard deviation.
[a]Final height achieved versus insurance reasons, P <.0001; final height achieved versus all other reasons, P <.0001; insurance reasons versus patient/caregiver decision, P <.0001; insurance reasons versus all other reasons, P <.0001; patient/caregiver decision versus all other reasons, P = .0023.
[b]Final height achieved versus insurance reasons, P <.0001; final height achieved versus all other reasons, P = .0081; insurance reasons versus patient/caregiver decision, P <.0001; insurance reasons versus all other reasons, P = .0002; patient/caregiver decision versus all other reasons, P = .0189.
[c]Final height achieved versus all other reasons, P = .0468.
[d]Insurance reasons versus patient/caregiver decision, P = .0003.

(0.1%) were collectively included in the other category.

The mean ± SD treatment duration was 46 ± 21 months for final height achieved, followed by patient and caregiver decision (35 ± 15 months), insurance issues (32 ± 21 months), and other (31 ± 18 months). Overall, no difference in treatment duration (mean ± SD) was observed between patients with IGHD (37 ± 19.9 months, n = 778) or MPHD (39 ± 26.7 months, n = 48). However, in patients who discontinued GH due to final height achieved, those with MPHD had a longer duration of treatment (57 ± 35.4 months, n = 13) than patients with IGHD (45 ± 19.6 months, n = 275); this was likely due to the younger age of MPHD patients at treatment start, but may also have been due to delayed entry into puberty of individuals with MPHD. The overall mean duration of GH treatment among all categories was 37 ± 20.3 months (n = 826).

Age- and Sex-Adjusted Persistence With GH Therapy

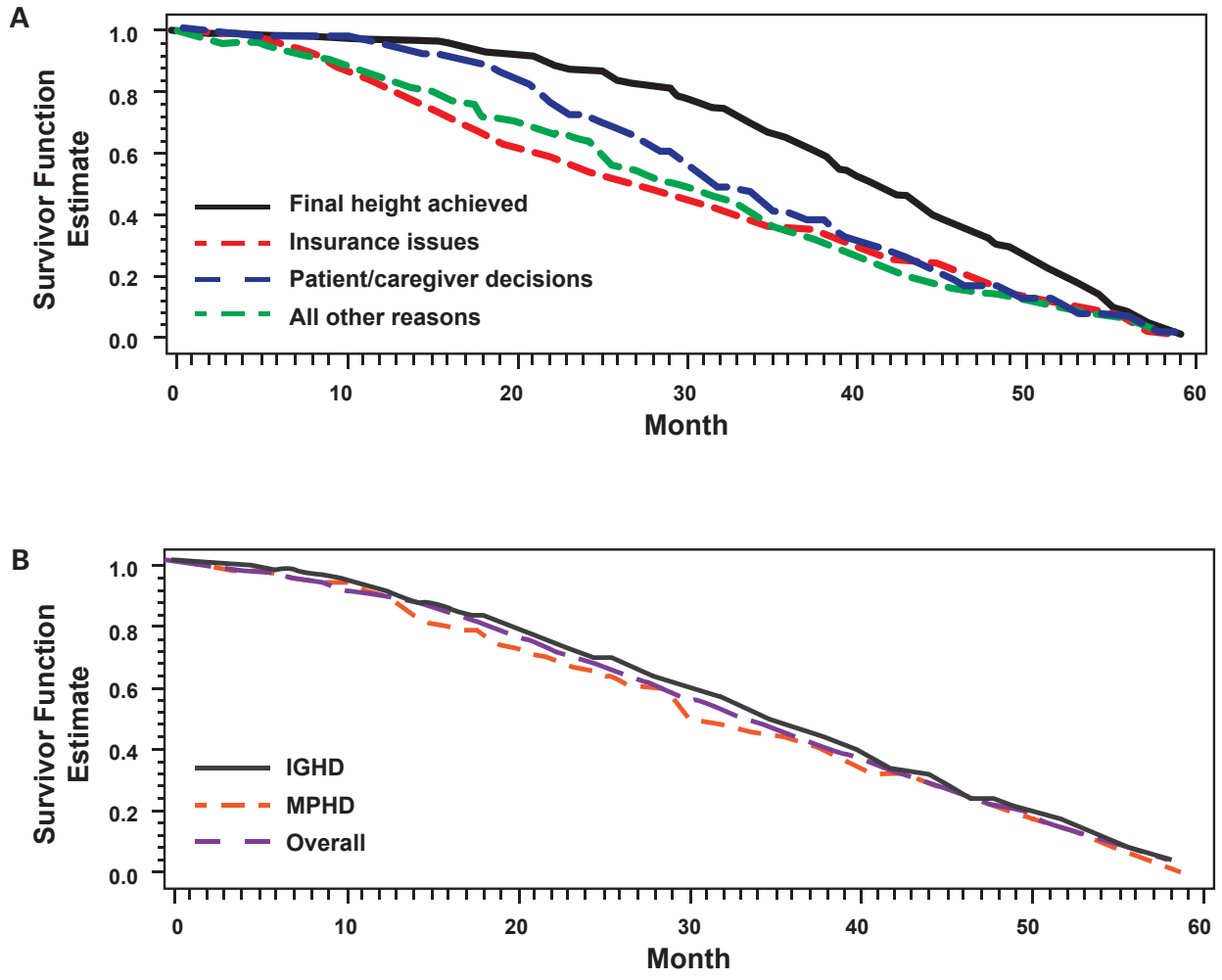
After adjusting for baseline age and sex, differences in persistence with GH therapy over time among the 4 discontinuation categories were estimated from analysis of survival curve functions (**Figure 1A**). Category comparisons indicated that patients who discontinued therapy due to final height being achieved were more persistent than patients in the other categories of insurance issues (P <.0001), other (P <.0001), and patient and caregiver decision (P = .0009). Patients who discontinued therapy due to patient and caregiver decision were also more persistent than patients who discontinued therapy due to insurance issues (P = .0086). Thus, patients who discontinued because of insurance issues or other reasons were the least persistent with GH treatment. Patients with either IGHD or MPHD were equally persistent with GH therapy (**Figure 1B**; P = .6953).

Height Outcome by Reason for Discontinuation

Overall, mean HSDS increased significantly in the combined IGHD and MPHD groups from baseline to the year 3 visit (**Table 3**) in patients in all discontinuation categories (**Figure 2A**, P <.0001). Pairwise comparisons showed that mean HSDS at last visit for patients who discontinued due to final height achieved (−0.6 ± 0.91, n = 288) was significantly higher than the mean HSDS for other (−1.3 ± 1.06, n = 173; P <.0001), insurance issues (−1.2 ± 0.90, n = 231; P <.0001), and patient and caregiver decision (−0.9 ± 1.19, n = 134; P = .0222). At year 3, prior to GH discontinuation and the last visit, the mean HSDS for final height achieved (−0.7 ± 0.82, n = 197) was significantly higher than that for other (−1.2 ± 1.06, n = 65; P = .0006) and insurance issues (−1.0 ± 0.83, n = 79; P = .0149), but it was not significantly higher than that for patient and caregiver decision (−1.0 ± 0.95, n = 51; P = .0679).

The mean corrected HSDS in the combined IGHD and MPHD groups also increased significantly from baseline to the year 3 visit (Table 3) in patients in all categories (**Figure 2B**, P <.0001). Pairwise comparisons showed that mean corrected HSDS at last visit for patients who discontinued due to final height achieved (−0.3 ± 0.98, n = 258) was significantly higher than the mean corrected HSDS for other (−1.0 ± 1.07, n = 139; P <.0001), insurance issues (−0.9 ± 1.03, n = 190; P <.0001), and patient and caregiver decision (−0.5 ± 1.18, n = 110; P = .05). Mean corrected HSDS for final height achieved at year 3 (−0.3 ±

Figure 1. Persistence Rates for Growth Hormone Therapy by Reason for Discontinuation (A) and by Diagnosis (B)[a]



IGHD indicates idiopathic growth hormone deficiency; MPHD, multiple pituitary hormone deficiency.
[a]Panel A: Final height achieved versus insurance reasons (P <.0001); final height achieved versus all other reasons (P <.0001); final height achieved versus patient/caregiver decision (P = .0009); patient/caregiver decision versus insurance reasons (P = .0086). Panel B: IGHD versus MPHD diagnostic groups (P = .6593).

0.90, n = 179) was significantly higher than that for other (−1.0 ± 1.03, n = 55; P = .0006) and insurance issues (−0.6 ± 0.81, n = 63; P = .0269), but it was not significantly higher than that for patient and caregiver decision (−0.5 ± 1.07, n = 39; P = .23).

A higher percentage of children in the final-height-achieved discontinuation category reached HSDS greater than −2 at year 3 (96.4%) compared with children in the other 3 discontinuation categories: patient and caregiver decision (94.1%), insurance issues (88.6%), and other (78.5%). Annualized growth rates for the 6 to 12 months prior to discontinuation showed that children who discontinued due to final height achieved had the lowest HV (3.4 ± 2.06 cm/y, n = 249) compared with children in the other categories (Table 3); this is consistent with children in the final-height-achieved group approaching their final height and fusion of their epiphyseal growth plates.

DISCUSSION

Persistence and adherence are necessary to ensure that GHD patients who receive GH treatment attain their genetic height potential.[8,13] Good adherence to prescribed regimens, including GH therapy, wanes beyond 2 years of treatment.[10,13,16,17] Good medication adherence among patients is considered to range from 80% to 95% of prescribed doses taken.[16] Objective assessments of poor adherence to GH have included analyses of prescription data; patient/caregiver questionnaires, which were followed up with serial clinical assessments to capture

Table 3. Height Outcomes at Year 3 for Combined GH-Naïve Patients With IGHD or MPHD Who Discontinued Treatment

Discontinuation Reason and Time Point	HSDS, Mean ± SD (n)	Corrected HSDS, Mean ± SD (n)	Percent HSDS ≥−2 (n)	HV, cm/y (n)
Final height achieved				3.4 ± 2.06 (249)
Baseline	−2.1 ± 0.83 (288)	−1.8 ± 1.00 (258)	41.0% (118)	
Year 3	−0.7 ± 0.82 (197)	−0.3 ± 0.90 (179)	96.4% (190)	7.0 ± 2.89 (195)
P	<.0001	<.0001		
Insurance reasons				
Baseline	−2.2 ± 0.80 (231)	−1.8 ± 1.00 (190)	37.7% (87)	
Year 3	−1.0 ± 0.83 (79)	−0.6 ± 0.81 (63)	88.6% (70)	5.2 ± 4.17 (107)
P	<.0001	<.0001		
Patient/caregiver decision				
Baseline	−2.1 ± 0.95 (134)	−1.8 ± 1.05 (110)	46.3% (62)	
Year 3	−1.0 ± 0.95 (51)	−0.5 ± 1.07 (39)	94.1% (48)	5.2 ± 3.33 (135)
P	<.0001	<.0001		
All other reasons				
Baseline	−2.20.89 (173)	−1.91.07 (139)	39.3% (68)	
Year 3	−1.2 ± 1.02 (65)	−1.0 ± 1.03 (55)	78.5% (51)	–
P	<.0001	<.0001		

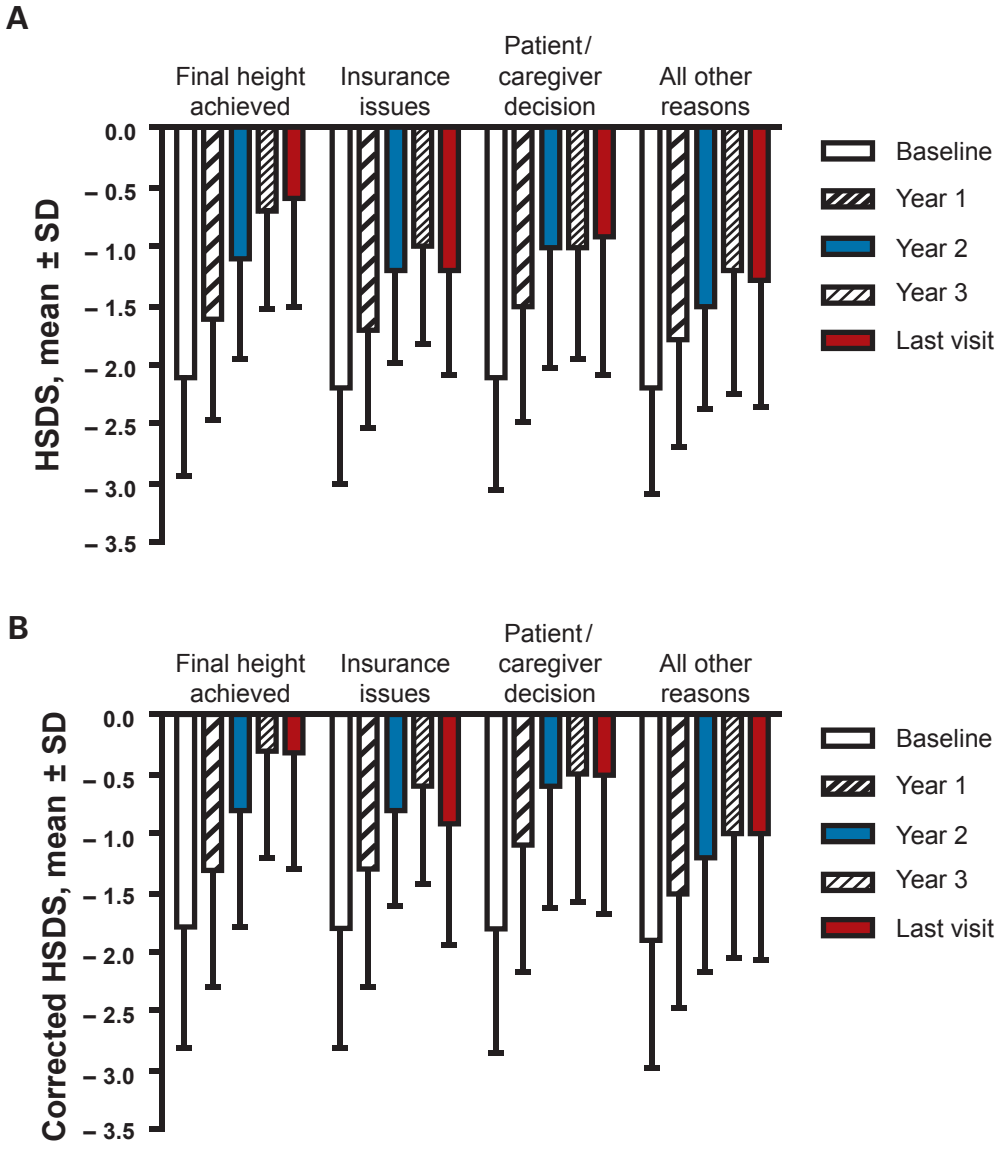
Corrected HSDS indicates HSDS minus target HSDS; GH, growth hormone; HV, height velocity for the 6 to 12 months prior to discontinuation; HSDS, height standard deviation score; IGHD, idiopathic growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SD, standard deviation.

HSDS and HV; and the association between HV SDS and the number of GH vials requested or returned empty.[9,11,12] By any measure, outcomes have consistently shown that significantly greater linear growth and attainment of genetic height potential are positively associated with adherence to prescribed GH therapy.[9,11,12] Adherence to GH regimens is important, but persistence may be even more critical because gaps in therapy that lead to delayed or missed GH doses over the prescribed duration of time from therapy initiation to discontinuation cause suboptimal response to GH treatment that negatively impacts growth outcomes.[8,9,12,13]

In the current study, patients who were most persistent with GH therapy (ie, those who reached the category of final height achieved) attained a statistically significant increase in linear growth with a final HSDS of –0.6 compared with –2.1 at baseline. This result is consistent with increasing linear growth patterns to near-adult height in prepubertal children with GHD or MPHD from other large patient registry databases.[7,18] Current analyses of data from the ANSWER Program showed that patients who reached final height achieved were the most persistent with GH therapy and achieved a corrected HSDS of −0.3 compared with a baseline corrected HSDS of −1.8; that indicates that these patients, on average, had reached an adult height consistent with their genetic height potential. This result compares favorably with published target adult or genetic HSDS values within normal standards (±0.5) for North American adults and children.[13,19] The fact that children in the final-height-achieved group had the slowest HV in the period prior to discontinuation but had the highest percentage in the normal adult height range also provides evidence that final height achieved was the primary reason for discontinuing therapy. Although MPHD patients in the final-height-achieved group had a longer duration of treatment, overall persistence was similar between patients with IGHD or MPHD, regardless of the reason for discontinuation.

The second-most common reason for patients discontinuing GH therapy was insurance issues; patients in this category were less persistent with GH treatment. Although patients discontinuing GH for insurance issues did not achieve height outcomes comparable to those of patients in the other categories, a shorter duration of treatment in this cohort may be a factor in their decreased height outcomes. However, even at the same duration of treatment at year 3, children in the final-height-achieved group attained greater HSDS and corrected HSDS than

Figure 2. Height Outcomes in Patients Over Time for All Patient Categories of Reason for Discontinuation of Growth Hormone Treatment at Baseline, Year 1, Year 2, Year 3, and Last Visit: HSDS (A) and Corrected HSDS (B)



Corrected HSDS indicates HSDS minus target HSDS; HSDS, height standard deviation score; SD, standard deviation.

children in insurance-issues group and the other group; the final-height-achieved group also had the highest percentage of patients reaching an HSDS greater than −2. These results could imply that patients in the insurance-issues and other categories may already have had some adherence challenges related to insurance or other reasons. We were unable to evaluate the long-term effects of interrupted GH therapy in this cohort due to a lack of follow-up data once these patients were discontinued from the registry.

Additionally, although the baseline HSDSs for groups characterized by reason for discontinuation were comparable, there did appear to be differences in the mean age and proportion of males in the insurance-issues group compared with the other 3 groups. For these reasons, it is difficult to conclude that ultimate adult height values would differ among these groups. However, given the younger baseline age and bone age of the insurance-issues group, it might be expected that these patients would have shown a better growth response, which was not the case either at the last visit or after 3 years of treatment.

With pediatric patients it is difficult to conduct appropriately powered clinical studies with rigorous objective

measures to assess the effect of adherence or persistence with GH therapy on long-term height outcomes. Studies of the effect of adherence and persistence on growth outcomes among patients with IGHD or MPHD are difficult because databases that monitor GH utilization in this population may include different dosing regimens (ie, weight based, fixed, pubertal, not following US Food and Drug Administration dosing guidelines) or fail to record data (ie, auxologic, dosing, adherence, reasons for discontinuation, gaps in therapy) in registry or claims databases. Infrequent patient visits to the specialist can also lead to inadequate data entry related to adherence and persistence. Such data would enable more effective analyses of large sample sizes and calculations of adherence and persistence using standardized methods.[8] In the present study, we were limited to analyzing patient- and physician-reported data as a means to determine rates of persistence with GH treatment in pediatric patients with IGHD or MPHD.

Other factors correlating with the level of adherence to GH therapy are patient motivation,[11,17] psychological/emotional problems,[11,17] social and daily living problems,[11,17] patient/caregiver understanding of the consequences of noncompliance with prescribed treatment,[20,21] appropriate training of patients and caregivers in administration of GH,[21] family socioeconomic status and parental educational level,[22] choice of drug-delivery device,[23,24] and technical-handling issues with the delivery device.[5,9,10,17,25] In addition, it is likely that healthcare system factors impact adherence and persistence (eg, insurance prior authorization and recertification processes, medication-delivery issues, access to pediatric specialists). Increasing recognition of the factors that affect adherence and persistence with GH treatment has led to renewed interest in the development of clinical practice strategies that could help children and their families overcome these challenges.[17] Improved communication between providers, insurance carriers, and specialty pharmacies could raise provider awareness of issues that impact patient adherence and persistence, and allow providers to address these barriers.

Although recent reviews have focused on nonadherence as a major factor that can influence the outcome of GH therapy,[9-13,17] results from our study suggest that GH therapy is also often discontinued because of insurance issues that are independent of personal or medical reasons. The effects of insurance-mandated brand switches during the course of pediatric GH treatment are poorly understood, but a recent survey of physicians found that such switches may contribute to decreased adherence and increased patient anxiety.[26] Switching to a different GH product may lead to worse growth outcomes due to the possibility of dosing errors and patient confusion, new potential for immunogenicity, and adverse effects such as injection site pain or burning.[26]

Changes in insurance coverage for GH therapy can be due to a change of carriers, an insurance company switch to approval through a pharmacy benefit manager, a change in the insurance criteria for GH approval, a retrospective review of previously approved cases with new approval criteria, or a change in insurance criteria for stopping therapy. When an insurance carrier changes, a new coverage application is required and the child may no longer qualify based on the new carrier's coverage criteria. If an insurance company rejects a patient's treatment, physicians and family members may then need to become involved in a time-consuming appeals process; this may cause a lack of persistence or early termination of therapy, leading to worse growth outcomes.

A lack of follow-up data and a lack of height-outcomes comparisons for patients who discontinued therapy with somatropin injection after receiving GH treatment for the same length of time are limitations of this analysis. Individuals may have continued therapy on another GH drug and achieved comparable height outcomes; currently, however, there is no way to track patients who are enrolled in different manufacturer-based registries. Future research is needed to explore the impact of therapy discontinuation on long-term height outcomes in children treated with GH.

Improving payer processes so that GH therapy will continue to be approved, while minimizing mandated switches to a different GH product, may help ensure adherence and persistence with GH therapy and optimize growth outcomes.[26] Improvements in the approval and formulary-change processes could include notifying patients and providers about impending formulary changes and changes in coverage criteria, educating patients and families about the importance of persistence in order to achieve ultimate height outcomes, developing industry-wide insurance guidelines for the approval and continuation of GH therapy, and creating similar application forms and appeals processes among insurers.

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